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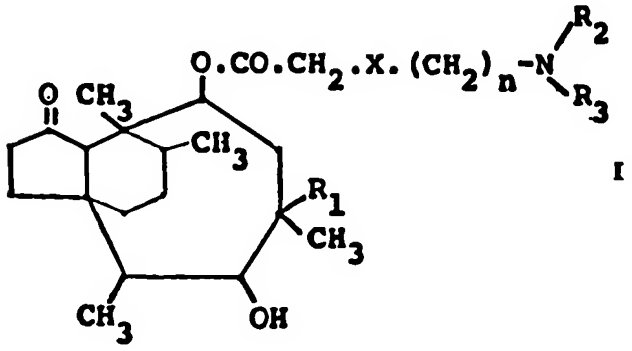
Title: Method for producing new pleuromutiline derivatives

Holder: Sandoz AG, Basel

Represented by:

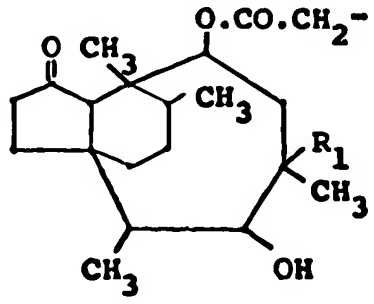
Inventors: Dr. Helmut Egger, Vienna (Austria) and Dr. Hellmuth Reinshagen, Hartheim-Feldkirch (Federal German Republic)

The invention concerns a method for producing new pleuromutiline derivatives of formula I



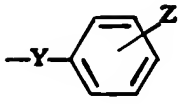
I

In which R_1 stands for the ethyl or vinyl group, n stands for a whole number from 2 through 5, and X stands for sulfur, the group >N-R_4, wherein R_4 means hydrogen or a grouping of formula II



II

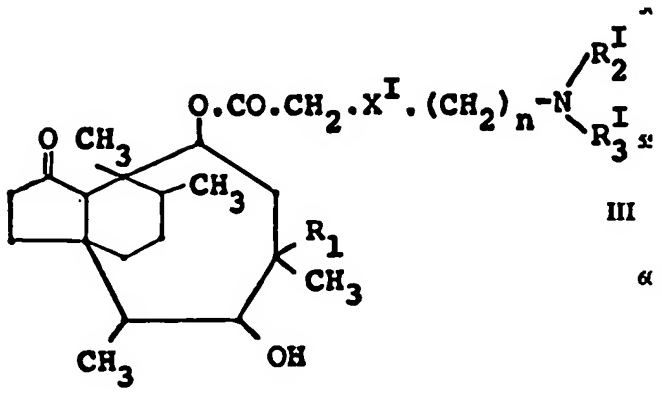
In which R_1 has the meaning above, or a



group

in which, if Y and Z are the same, both stand for sulfur or, if Y and Z are different, they mean sulfur or oxygen, and R_2 and R_3, jointly with the nitrogen atom, form a piperazinyl radical whose second nitrogen atom is substituted by an R_5 group wherein
R_5 stands for a lower (lower acyloxy)alkyl group, or wherein, if X stands for >N-R_4 and n stands for 2, R_2 and R_4, jointly with the two nitrogen atoms, form a piperazinyl radical wherein R_3 stands for a lower (lower acyloxy)alkyl group and their acid addition salts.

The method is characterized in that compounds of formula III



III

In which R_1, X and n have the meaning above and R_2^I and R_3^I, jointly with the nitrogen atom, form a piperazinyl radical whose second nitrogen atom is substituted by an R_5^I group wherein R_5^I stands for a lower hydroxyalkyl group or wherein, if X stands for >N-R_4 and n stands for 2, R_2^I and R_4 , jointly with the two nitrogen atoms, form a piperazinyl radical wherein R_3^I stands for a lower hydroxyalkyl group, are reacted with a compound of formula IV

$$A\text{-}R_5 \qquad \text{IV}$$

wherein A stands for a haloformyl or $R_5CO{\bullet}O{\bullet}CO$ group and R_5 stands for a lower alkyl group, and the compounds of formula I obtained are converted as desired into their acid addition salts.

The starting products are described in the original patent 575 375. Furthermore, the compounds of formula I have the same pharmacological properties as the compounds of formula I described in original patent 575 375 and can therefore be used in the same way.

The tertiary amino compounds of formula I obtained can be quaternated by reaction with a quaternation agent.

Example 1

14-deoxy-14-{[2-(4-propionyloxyethyl)-piperazino]ethyl-mercaptoacetoxy} mutiline

0.50 g of 14-deoxy-14-{[2-(4-hydroxyethyl)piperazino]-ethylmercaptoacetoxy} mutiline are boiled with reflux for 2 hours in 5 ml dichloromethane with 0.20 g propionyl chloride. After cooling, the crystalline dihydrochloride is precipitated by the addition of ethereal hydrochloric acid and dilution with absolute ether. The salt is drawn off and washed with ether. Melting point: 182-187°C.

Example 2

14-deoxy-14-{[2-(4-pivaloyloxyethyl)-piperazino]ethyl-mercaptoacetoxy} mutiline

0.50 g of 14-deoxy-14-{[2-(4-hydroxyethyl)piperazino]-ethylmercaptoacetoxy} mutiline are boiled with reflux for 4 hours in 5 ml dichloromethane with 0.15 g pivaloyl chloride. After cooling, the crystalline dihydrochloride is precipitated by the addition of ethereal hydrochloric acid and dilution with absolute ether. The salt is drawn off, briefly washed with absolute ether and vacuum-dried. The substance hydrolyzes very readily to the starting material in the presence of water.

Example 3

14-deoxy-14-{[2-(4-acetoxyethyl)piperazino]ethyl-mercaptoacetoxy} dihydromutiline

0.50 g of 14-deoxy-14-{[2-(4-hydroxyethyl)piperazino]-ethylmercaptoacetoxy} dihydromutiline are allowed to stand for 2 hours with 1.5 ml acetic anhydride at room temperature, then diluted with 10 ml water and stirred for 1 hour at room temperature to destroy the excess acetic anhydride. The solution is extracted 3 times with ether, made alkaline and then extracted with ethyl acetate. The dihydrochloride is precipitated from the concentrated solution with ethereal hydrochloric acid as described above. Melting point: 133-135°C.

Example 4

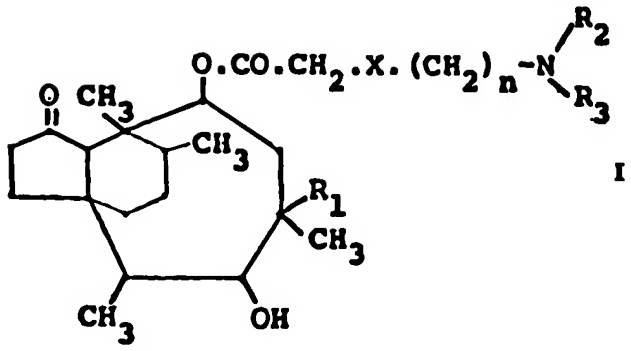
14-deoxy-14{[2-(4-acetoxyethyl)piperazino]ethylmercaptoacetoxy} mutiline

4.0 g 14-deoxy-14-{[2-(4-hydroxyethyl)piperazino]ethylmercaptoacetoxy} mutline are mixed with 10 ml acetic anhydride with ice cooling and then stirred for 5 hours at room temperature. The mixture is then poured into 150 ml of cold water, stirred for 1 hour and extracted 3 times with ether. The ether phases are discarded and the aqueous phase is made alkaline with 10 N aqueous sodium hydroxide solution with cooling. The free base precipitated is absorbed in ethyl acetate. After the solution is dried over magnesium sulfate and the solvent is evaporated off, the pure base remains and is converted into hydrochloride with ethereal hydrochloride. Softening point 137-140°C.

5.92 g of the raw base of the title compound are absorbed in 80 ml absolute dichloromethane and mixed with the solution of 2.40 g maleic acid in 15 ml absolute methanol. The bis(hydrogen maleinate) crystalline product is precipitated by slowly adding absolute ether. It is then drawn off and washed with ether. Melting point of the bis(hydrogen maleinate) 142-144°C.

CLAIMS

I. Method for producing compounds of formula I



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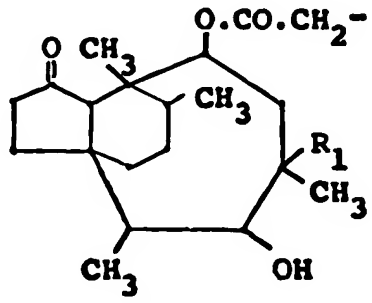

II

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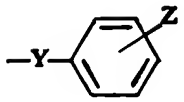

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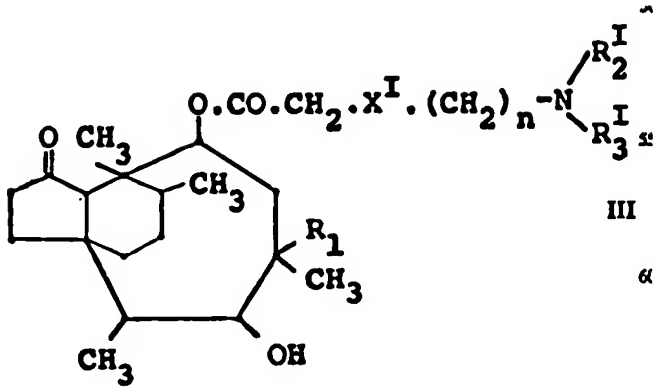
characterized in that compounds of formula III



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$$A\text{-}R_5 \qquad \text{IV}$$

wherein A stands for a haloformyl or $R_5CO{\bullet}O{\bullet}CO$ group and R_5 stands for a lower alkyl group, and the compounds of formula I obtained are converted as desired into their acid addition salts.

II. Use of the pleuromutilines of formula I obtained with the method according to claim I for producing their quaternated salts, characterized in that tertiary amino compounds obtained are quaternated with a quaternation agent.

Note by the Swiss Office for Intellectual Property

If parts of the description do not agree with the definition of the invention given in the claims, bear in mind that, under Article 51 of the Patent Law, the claims determine the actual area of validity of the patent.